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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/876,187	06/05/2001	Stuart A. Lipton	P-LJ 4714	5845
23601	7590	11/28/2003		
CAMPBELL & FLORES LLP 4370 LA JOLLA VILLAGE DRIVE 7TH FLOOR SAN DIEGO, CA 92122			EXAMINER FALK, ANNE MARIE	
			ART UNIT 1632	PAPER NUMBER

DATE MAILED: 11/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/876,187

Applicant(s)

LIPTON ET AL.

Examiner

Anne-Marie Falk, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 May 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-57 is/are pending in the application.
- 4a) Of the above claim(s) 21-57 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-20 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

DETAILED ACTION

Claims 1-57 are pending in the instant application.

Applicants election, with traverse, of Group I, Claims 1-9 and 12-20, is acknowledged. In view of Applicants' traversal arguments, Groups I and II are rejoined.

Thus, Claims 1-20 are examined herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method of differentiating progenitor cells, particularly embryonic stem cells and hematopoietic stem cells. The claims encompass *in vivo* and *in vitro* applications of the method.

Even as late as 2001, the art acknowledged that gene transfer into human hematopoietic stem cells was problematic (Hanazono et al., 2001). The claimed invention must be enabled at the time of filing. However, the priority date of this application is June 5, 2000. Thus, the instant specification must provide an enabling disclosure for the claimed invention as of this priority date.

The specification fails to provide an enabling disclosure for the genetic modification of human ES cells. The recent literature addresses the difficulties encountered in attempting to transfect human ES cells. Zwaka et al. (2003) points out that there are significant differences between mouse and human ES

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cells and that “[h]igh, stable transfection efficiencies in human ES cells have been difficult to achieve, and, in particular, electroporation protocols established for mouse ES cells work poorly in human ES cells” (abstract). Thus, it is clear that the behavior of mouse ES cells is not predictive of human ES cells. In April 2001, Eiges et al. compared the efficiency of several different transfection protocols for human ES cells. The reference demonstrates use of the transfection protocol of ExGen 500 to transfect human ES cells. However, the instant specification teaches the use of adenovirus transduction for the genetic modification of human ES cells. Example 6 of the specification describes the transfection of human ES cells with an adenovirus carrying the β -galactosidase reporter gene. Although the disclosure states that “[s]taining for expression of the β -galactosidase marker gene was performed,” no results are provided with regard to the detection of β -galactosidase-expressing cells. Thus, at the time of filing, methods for successfully transfecting human ES cells were not known. The teachings of Eiges et al. (2001) would not have been available to the skilled artisan as of the filing date of this application which is July 27, 2000.

Regarding gene transfer into human HSCs, even as late as 2001, the art acknowledged that gene transfer into human hematopoietic stem cells was problematic (Hanazono et al., 2001). The claimed invention must be enabled at the time of filing. However, the priority date of this application is June 5, 2000. Thus, the instant specification must provide an enabling disclosure for the claimed invention as of this priority date.

The specification contemplates that transfecting the ES cells with a nucleic acid encoding an MEF2 and contacting the cells with a differentiating agent will be sufficient to direct the cells to differentiate *in vivo* or *in vitro* into the appropriate cell type and functionally integrate into the tissue into which they are implanted. However, the state of the art for *in vivo* differentiation of ES cells is undeveloped. While much work has been done to develop techniques for the directed differentiation of ES cells *in vitro* to produce desired cell types, little is known about the behavior of these cells *in vivo* or

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how they will interact with the local environment when implanted into adult tissues. Jackowski (1995) details the limitations and unpredictability associated with the transplantation of neural tissue.

Given the lack of applicable working examples, the limited guidance provided in the specification, the broad scope of the claims with regard to the wide variety of stem or progenitor cell types that could be used, and the unpredictability for producing cells suitable for therapeutic transplantation, undue experimentation would have been required for one skilled in the art to practice the claimed method of the invention to produce useful cell compositions.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, William Phillips, whose telephone number is (703) 305-3482.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk
ANNE-MARIE FALK, PH.D.
PRIMARY EXAMINER